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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,846	02/09/2006	Tatsuo Hoshino	21414 US C0381435/0186340	2015

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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	**PAPER NUMBER**
1652	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,846	HOSHINO ET AL.	
	Examiner	Art Unit	
	IQBAL H. CHOWDHURY	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/5/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 1-2, 4-5 and 8 are pending in this application.

In response to a previous Office action, a final action (mailed on August 7, 2007), Applicants filed a response and amendment received on February 5, 2008, amending claim 1 and canceling claims 6-7 is acknowledged. Claim 3 remain cancelled.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 5, 2008 has been entered.

Claims 1-2, 4-5 and 8 are under consideration and will be examined herein.

Applicants' arguments filed on February 5, 2008, have been fully considered but are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Maintained- Claims Rejections- 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Previous rejection of Claims 1-2, 4-5 and 8 under 35 U.S.C. 103(a) as being unpatentable over Misawa et al. (Canthaxanthin biosynthesis by the conversion of methylene to keto groups in a hydrocarbon beta-carotene by a single gene, Biochem Biophys Res Commun. 1995 Apr 26; 209(3): 867-76, see IDS) in view of Hoshino et al. (US Patent 6,365,386 B1, issue date 4/2/2002, see IDS) is maintained. This rejection has been discussed at length in the previous office action. This rejection is maintained for the following reasons.

Instant claims are drawn to a process for producing canthaxanthin and echinenone, which comprises cultivating in an aqueous nutrient medium at a pH range of 5 to 7, temperature range of 18 to 22oC for 48 to 350 hrs, a recombinant *Xanthophyllomyces dendrorhous (Phaffia*

rhodozyma) microorganism that comprises a polynucleotide sequence that encodes a β-carotene ketolase, wherein β-carotene accumulates in the medium under aerobic conditions, and isolating carotenoids from the recombinant microorganism or from the medium, wherein the polynucleotide sequence is originated from a microorganism which is selected from the group consisting of *Agrobacterium aurantiacum, Alcaligenes* PC-I, *Paracoccus marcusii* MH1, a gram-negative bacteria E-396 (FERM BP-4283), and *Haematococcus pluvialis.*

As discussed previously, Misawa et al. (BBRC) teach a method of producing canthaxanthin and echinenone from beta-carotene by using a recombinant E. coli comprising beta-carotene ketolase gene (crtW) from Alcaligenes PC-I, which is 100% identical to the beta-carotene ketolase gene of the instant application. Misawa et al. also teach cloning said gene in expression vector, which is under the control of a promoter, transform an E. coli and culturing the said recombinant microorganism at 28oC at pH in which E. coli grows well, i.e. pH 7-8 (which is well known in the art) and produced canthaxanthin and echinenone (see whole document). Misawa et al. do not teach the use of transformed Phaffia rhodozyma by the said gene for producing canthaxanthin and echinenone.

Hoshino et al. disclose a process for producing astaxanthin from beta-carotene in Phaffia rhodozyma ATCC96815 comprising all the genes required to produce astaxanthin i.e. beta-carotene ketolase (crtW) (the same gene as claimed by the instant application) and crtZ gene and produce all the intermediates including canthaxanthin, and echinenone as well as astaxanthin (see col.4 2nd par.). Hoshino et al. also disclose to use a mutant strain of Phaffia rhodozyma, which is blocked for the astraxanthin production i.e. this mutant strain will produce mainly canthaxanthin, and echinenone. Hoshino et al. further disclose the process, wherein the

cultivation of the recombinant microorganism is performed at 20oC for over-night (about 24 hr) at a pH wherein the recombinant microorganisms grow well. Hoshino et al. do not disclose culturing the recombinant microorganism for 48-350 hours.

Summarizing, what are claimed, 1) a process for producing canthaxanthin/echinenone, which is intermediate of astaxanthin biosynthesis from beta-carotene; 2) by using a microorganism *Xanthophyllomyces dendrorhous (Phaffia rhodozyma)* comprising a gene encoding beta-carotene ketolase gene of crtW from a *Alcaligenes* PC-1 in aerobic condition; 3) cultured the microorganism at pH 5-7, temperature 18-22oC for 48-350 hrs.

Summarizing, the teachings of prior art, 1) Misawa et al. (BBRC), teach a process for producing canthaxanthin/echinenone by using a transformed E. coli comprising a gene encoding beta-carotene ketolase of crtW from a *Alcaligenes* PC-1, which is 100% identical to instant application beta carotene ketolase gene and same source, i.e. *Alcaligenes* PC-1 as disclosed by the instant application, wherein the cells are cultured at 28oC at a pH in which E. coli grows well i.e. pH 7-8 (which is well known in the art); and 3). Hoshino et al. teach a process for producing astaxanthin from beta-carotene in Phaffia rhodozyma (same strain used by the instant application) comprising beta-carotene ketolase (crtW), which produces canthaxanthin from beta-carotene and crtZ gene encoding an enzyme which converts canthaxanthin to astaxanthin by cultivating said microorganism at 20oC for overnight (i.e. 24 hr). The three prior arts clearly taught all the limitation including said method of producing canthaxanthin.

Since, Misawa et al. (BBRC) teach the whole process of the claimed invention except using Phaffia rhodozyma, for producing canthaxanthin from beta-carotene comprising beta-carotene ketolase of crtW from a *Alcaligenes* PC-1, therefore, one of ordinary skill in the art

would have been motivated to use Phaffia rhodozyma instead of E. coli as taught by Hoshino et al. to produce canthaxanthin and echinenone because Phaffia, red yeast usually used for the microbiological production systems for natural astaxanthin, which comprises sufficient amount of natural substrate beta-carotene. Furthermore, Hoshino et al. clearly teach that substantial amount of astaxanthin was produced by culturing the recombinant microorganism for 24 hours, and it is well known and common practice or knowledge in the art to increase or decrease the culturing time or temperature to obtain maximum amount of product. Therefore, one of ordinary skilled in the art would obviously test by culturing 48 hours or beyond of said recombinant microorganism to see whether increased amount of canthaxanthin is produced.

It would have been obvious to one to ordinary skill in the art at the time of the invention was made to combine the teaching of Misawa et al. (BBRC) and Hoshino et al. to produce canthaxanthin and echinenone from beta-carotene by using the beta-carotene ketolase gene (crtW) of Misawa et al. to transform the Phaffia rhodozyma of Hoshino et al. to produce canthaxanthin and echinenone by using the methods of Misawa et al. and Hoshino et al.

One of ordinary skill in the art would have been motivated to use Phaffia rhodozyma instead of E. coli to produce canthaxanthin and echinenone because Phaffia, red yeast usually used for the microbiological production systems for natural astaxanthin comprises sufficient amount of natural substrate beta-carotene. One of ordinary skill in the art would have a reasonable expectation of success because using recombinant Phaffia rhodozyma for producing canthaxanthin and echinenone is customary and widely used in the art for the biosynthesis of xanthophylls such as canthaxanthin, echinenone, astraxanthin and zeaxanthin from beta-carotene.

Applicants' arguments:

Applicants in his lengthy arguments argue that with a view towards furthering prosecution, claim 1 has been amended to recite "a process for producing canthaxanthin and echinenone, which comprises cultivating in an aqueous nutrient medium *a recombinant Xanthophyllomyces dendrorhous (Phaffia rhodozyma)* microorganism that comprises a polynucleotide sequence that encodes a β-carotene ketolase, wherein β-carotene accumulates in the medium under aerobic conditions and *wherein the cultivation is carried out at a pH in the range of from 5 to 7 and at a temperature* in the range of from 18 to 22°C *for 48 to 350 hours,* and (b) isolating carotenoids from the recombinant microorganism or from the medium, wherein the polynucleotide sequence is originated from a microorganism which is selected from the group consisting of *Agrobacterium aurantiacum, Alcaligenes* PC-1, *Paracoccus marcusii* MH1, a gram-negative bacteria E-396 (FERM BP-4283), and *Haematococcus pluvialis."*

Applicants also argue that it is well settled that the Examiner bears the burden to set forth a *prima facie* case of unpatentability. If the PTO fails to meet its burden, then the applicant is entitled to a patent, and when patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO should include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the documents relied on by the Examiner as evidence of obviousness. *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (April 30, 2007) (the obviousness *"analysis should be made* explicit' and the teaching-suggestion-motivation test is "a *helpful insight'* for determining obviousness. Moreover, the factual inquiry whether to combine documents must be thorough and searching. And, as is well settled, the teaching, motivation, or suggestion to

combine "must be based on objective evidence of record. Applicants submit that the rejection is devoid of any evidence - or even argument - in support of the proposed combination and all that is there is a conclusory statement.

This is not found persuasive because the Examiner in his previous office actions clearly and explicitly established the rejection including teaching, suggestion, motivation and expectation of success by using two prior references (Misawa et al. and Hoshino et al.) and common knowledge for increase or decrease culturing temperature or culturing period to produce maximum product and combining the teachings of the prior arts are clearly permissible if combining prior art reference results to arrive the claimed invention (See *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (April 30, 2007)).

Applicant's amendments and arguments have been fully considered but are not deemed persuasive to overcome the rejection on obviousness issues.

The only current amendment of claim 1 is for pH range of "5 to 7" and temperature range of "18 to 22oC for 48 to 350 hours" than previously stated of pH range of "4 to 8", and temperature range of "15 to 26oC for 24 to 500 hours".

Summarizing, what are claimed, 1) a process for producing canthaxanthin/echinenone, which is intermediate of astaxanthin biosynthesis from beta-carotene; 2) by using a microorganism *Xanthophyllomyces dendrorhous (Phaffia rhodozyma)* comprising a gene encoding beta-carotene ketolase gene of crtW from a *Alcaligenes* PC-1 in aerobic condition; 3) cultured the microorganism at pH 5-7, temperature 18-22oC for 48-350 hrs.

Summarizing, the teachings of prior art, 1) Misawa et al. (BBRC), teach a process for producing canthaxanthin/echinenone by using a transformed E. coli comprising a gene encoding beta-carotene ketolase of crtW from a *Alcaligenes* PC-1, which is 100% identical to instant application beta carotene ketolase gene, which is isolated from same source, i.e. *Alcaligenes* PC-1 as disclosed by the instant application, wherein the cells are cultured at 28oC at a pH in which E. coli grows well i.e. pH 7-8 (which is well known in the art); and 2). Hoshino et al. teach a process for producing astaxanthin from beta-carotene in Phaffia rhodozyma (same strain used by the instant application) comprising beta-carotene ketolase (crtW), which produces canthaxanthin from beta-carotene and crtZ gene encoding an enzyme which converts canthaxanthin to astaxanthin by cultivating said microorganism at 20oC for overnight (i.e. 24 hrs).

The two prior arts clearly taught all the limitation including said method of producing canthaxanthin, which is not based on just for arguments but based on evidences such as the publications, the whole process for producing canthaxanthin, the microorganism, the gene, the temperature for culture, time period for culture and the product produced as canthaxanthin. Applicants' lengthy arguments are not consistent with the facts as provided by the Examiner. In addition, one of skilled in the art would try to change temperature range or incubation period to achieve maximum product formation from the teachings of Misawa et al. and Hoshino et al. and changing temperature range and incubation period is within the common knowledge of one of skilled in the art Applicants are reminded that this rejection is not 102 but obvious type of 103 rejection, where primary reference teach substantial part of the claimed invention, and the remaining part is taught by secondary or tertiary reference and there is clear motivation to one of ordinary skilled in the art to arrive the claimed invention. It is just not correct to argue why the

secondary or tertiary reference does not teach substantial part of the claimed invention. Besides, **Supreme Court** decision on *KSR Int'l v. Teleflex, Inc.* further strengthen the TSM test (teaching, suggestion and motivation) to combine the prior art elements to meet the claimed subject matter (see KSR Int'l Co. V. Teleflex, Inc., No 04-1350, US Apr. 30, 2007). The cited references teach all the limitation of claimed invention as well as a successful method for producing canthaxanthin and one of ordinary skill in the art would be motivated to combine the teachings of the references to arrive the claimed invention (see KSR Int'l Co. V. Teleflex, Inc., No 04-1350, US Apr. 30, 2007).

Since, Misawa et al. (BBRC) teach the whole process of the claimed invention except using Phaffia rhodozyma, for producing canthaxanthin from beta-carotene comprising beta-carotene ketolase of crtW from a *Alcaligenes* PC-1, therefore, one of ordinary skill in the art would have been motivated to use Phaffia rhodozyma instead of E. coli as taught by Hoshino et al. to produce canthaxanthin and echinenone because Phaffia, red yeast usually used for the microbiological production systems for natural astaxanthin, which comprises sufficient amount of natural substrate beta-carotene.

Therefore, It would have been obvious to one to ordinary skill in the art at the time of the invention was made to combine the teaching of Misawa et al. (BBRC) and Hoshino et al. to produce canthaxanthin and echinenone from beta-carotene by using the beta-carotene ketolase gene (crtW) of Misawa et al. (BBRC) to transform the Phaffia rhodozyma of Hoshino et al. to produce canthaxanthin and echinenone by using the methods of Misawa et al. and Hoshino et al., which is the claimed method of the instant application.

One of ordinary skill in the art would have a reasonable expectation of success because using recombinant Phaffia rhodozyma for producing canthaxanthin and echinenone is customary and widely used in the art for the biosynthesis of xanthophylls such as canthaxanthin, echinenone, astraxanthin and zeaxanthin from beta-carotene.

Thus, for the reasons above and as discussed previous office action, the rejection is maintained.

Conclusion

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury, Ph.D. whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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